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(54) Title: METHOD AND PREPARATION FOR BINDING ALDEHYDES IN SALIVA

(57) Abstract: The object of the invention is the use of compounds comprising one or more free sulphhydryl and amino groups for preparing a composition for locally binding aldehydes in saliva during smoking. The preferred compounds are cysteine and its derivatives. Also claimed are methods for decreasing the risk of smoking related cancers by using a composition of aldehyde binding substance(s), and a composition comprising aldehyde binding substance(s), characterized in that the composition is attached to or combined with a tobacco product, filter or holder.

Method and preparation for binding aldehydes in saliva

This invention relates to compositions for locally binding aldehydes in saliva during smoking. This invention relates also to a method, a kit and a tobacco product for decreasing the risk of developing cancer of the mouth and pharynx, larynx, oesophagus and stomach.

The main causes for upper digestive tract cancers are smoking and alcohol drinking. It has been estimated, for United States, that up to 80% of these cancers can be avoided by abstaining from alcohol drinking and smoking. Both alcohol drinking and tobacco have been shown to be independent risk factors for upper digestive tract cancers. Additionally, several epidemiological studies have confirmed that alcohol and tobacco interact in a multiplicative way to the cancer risk.

Acetaldehyde has been shown to be highly toxic and mutagenic under various experimental conditions. Epidemiological and biochemical studies on Asian heavy drinkers with aldehyde dehydrogenase-2 (ALDH2)-deficiency strongly suggest that acetaldehyde is a local and topical carcinogen in man. This deficiency results in the accumulation of acetaldehyde in saliva and also in markedly increased risk for upper GI-tract cancers.

We have shown that the mean *in vivo* concentration of salivary acetaldehyde in smokers, even without smoking, is about two times higher than in non-smokers after ethanol ingestion throughout the follow-up period of 160 minutes (Figure 1) (Salaspuro V, Salaspuro M. Synergistic effect of alcohol drinking and smoking on *in vivo* acetaldehyde concentration in saliva. Int J Cancer. 2004 Sep 10; 111(4):480-3; incorporated herein by reference). The area under the curve of salivary acetaldehyde in smokers was significantly higher than in non-smokers, 114.8±11.5 μM x h vs. 54.2±8.7 μM x h, respectively ($p=0.002$).

During the period of cigarette smoking the *in vivo* salivary acetaldehyde was increased to ten-fold from the levels derived from the sole ethanol ingestion. The salivary acetaldehyde increased immediately when the smoking was started but also declined rapidly after the cessation of smoking (Figure 2). The area under the curve of salivary acetaldehyde in smokers was seven times higher than in non-smokers and the difference was highly

significant, 369.5±12.2 μM x h vs. 54.2±8.7 μM x h, respectively (p=0.001). Differences between acetaldehyde concentrations are significant at all time points from 40 to 160 min ($p \leq 0.05$).

During active smoking the salivary acetaldehyde increased to 261.4±45.5 μM from the basal level. The salivary acetaldehyde increased immediately when the smoking was started but also declined rapidly after the cessation of smoking (Figure 3).

In patent literature it has been suggested that preparations, which are sucked or chewed in the mouth be used to decrease the effect of the harmful free radical compounds that are formed in connection with using tobacco products or being exposed to them. For example Hersch, US Pat No 5,922,346 and Hersch, WO 1999/000106 suggest a preparation, which comprises L-glutathione, selenomethionine, Vitamin C, Vitamin E, Vitamin A and L-cysteine. It was believed that L-glutathione is employed in protecting cells against oxidative stress by itself being oxidized. Thus, L-glutathione functions in combination with other enzyme systems in order to be reduced. L-cysteine delivery agent enhances endothelial cell reduced glutathione concentration and protects cells from damage from endogenous hydrogen peroxide. The patent publications suggest the use of the preparation in the form of chewable gum, tablet, lozenge or gel.

WO 02/36098 suggests the use of compounds comprising free sulphhydryl and/or amino group for locally binding acetaldehyde in the long term in saliva, the stomach or the large intestine. The compounds were mixed to a substance capable of releasing the acetaldehyde binding substances for at least 30 minutes in the conditions of the mouth, stomach or large intestine. The aim was to bind the increased acetaldehyde that occurs in connection with consuming alcoholic drinks or smoking.

There are several patent publications, which suggest compositions for reducing the blood level of acetaldehyde in order to prevent and treat hangover symptoms and prevent and treat liver damages associated with acetaldehyde. For example US 5,202,354 describes a composition comprising acetaldehyde binding substance, such as L-cysteine, ascorbic acid or salt thereof, a disulfide type thiamine derivative, or a salt thereof, and a cholagogue. US 4,528,295 describes a composition comprising methionine, vitamin B6 and potassium citrate.

Some patent publications suggest the addition of compounds capable of binding harmful substances from tobacco smoke during smoking to cigarette filters. For example, US Patent No. 5,829,449 suggests a composition for inclusion within a cigarette, cigar or pipe. The patent publication suggests that the composition can be included within the tobacco itself, a filter for filtering tobacco smoke once burned or within the paper or wrapper surrounding the tobacco product. The composition was said to be capable of reducing free radical damage to the oro-pharyngeal cavity, respiratory tract and lungs resulting from tobacco smoke. The composition included L-glutathione, and a source of selenium, such as L-selenomethionine or L-selenocysteine. The composition may comprise also L-cysteine and N-acetyl-l-cysteine.

U.S. Patent No. 4,532,947 suggests a filter for use in association with tobacco cigarette, which comprises non-toxic salts of 2-mercapto-alkalene sulphonates and/or cysteine and acetylcysteine. These compositions were to be added to cigarette filters or cigarette holders comprising a filter for the purposes of reducing toxic tobacco substances *in situ*, while smoking cigarettes.

The object of the invention is to provide a method and a composition for removing or decreasing the aldehyde content of the saliva during smoking. The composition and the method according to the invention are very useful in locally binding the increased amount of aldehyde that occurs in connection with smoking.

The invention is based on the surprising observation that the harmful amount of aldehydes locally occurring in saliva during smoking can be bound locally and quickly into a chemically safe form by using the preparations according to the present invention. As the substances that bind aldehydes are released in contents high enough to saliva throughout the period of effect of the aldehydes, the local concentration of aldehydes in saliva remains low. In this way, the local risk of contracting cancer caused by aldehydes decreases.

Aldehydes, in particular acetaldehyde present in tobacco smoke dissolves very quickly into saliva. It is of advantage, if the content of aldehydes dissolved in saliva can be lowered or the aldehydes entirely removed from saliva, before the aldehyde has caused damage to the mucosal cells in mouth or in upper respiratory tract or in stomach. The preparations of the

present invention are able to bind aldehydes very effectively in saliva keeping the aldehyde content much lower or at the level of non-smoking situation. The prior art does not suggest preparations or methods, which would keep the aldehyde concentration in saliva essentially lower or prevent the increase of aldehyde concentration during smoking.

According to the invention, compounds that comprise one or more free sulphhydryl and/or amino groups are used to prepare a composition, which is used to locally bind the aldehydes in saliva.

More specifically, the use according to the invention is characterized by what is stated in claim 1.

According to the invention, the composition comprises one or more substances that bind aldehydes optionally admixed with a carrier suitable for human consumption (sucking and/or chewing and/or keeping) in mouth. The substances contained by the composition are selected so that the substances are capable of binding aldehydes and are released within a short period of time.

This invention provides also a method according to claim 10 for decreasing the effect of aldehydes, which causes cancer, in human mouth, pharynx, larynx, oesophagus and stomach.

According to the method, the aldehydes contained in saliva are locally bound into a safe form by using a composition that releases one or more aldehyde-binding substances.

Furthermore, this invention provides a composition according to claim 19, a kit according to claim 28 and a tobacco product according to claim 30.

US 5,829,449 and US 4,532,947 disclose tobacco products and filters comprising compounds capable of binding harmful substances from tobacco smoke. However, it has turned out, that such filters are not capable of binding acetaldehyde, since the filter is too dry to let the reaction happen. The presence of acetaldehyde binding substances in tobacco product filters does not solve the problem of decreasing or removing the acetaldehyde or other aldehydes in saliva during smoking. The filters and other tobacco products disclosed

in US 5,829,449 and US 4,532,947 are aimed for binding harmful substances from tobacco smoke, not from saliva. Neither do products effecting systemically through blood circulation as described for example in US 4,528,295 and US 5,202,354 or which are aimed for preventing and ameliorating free radical damage induced by smoking as described in US 5,922,346, or products releasing acetaldehyde binding substances very slowly as described in WO 0236098, solve the problem.

So far, neither a method nor a preparation has been presented, which would locally decrease the acetaldehyde content of saliva during smoking. The preparations according to the prior art are aimed for systemically reducing blood acetaldehyde concentration and the alleged effect is based on the reaction of the effective substances to the acetaldehyde inside blood and/or cells. Preparations, which are aimed for preventing free radical damage as described for example in US 5,922,346 function locally and systemically through buccal mucosal absorption or through swallowing. Since the preparations comprise only low amounts of acetaldehyde binding substances, which in addition are involved in other chemical reactions, the local effect of acetaldehyde binding of the preparations in mouth is not significant. The preparations are also suggested to be used as a daily dosage, for example in the morning and in the evening, not specifically connected to smoking. Preparations affecting/increasing intracellular protection mechanisms, for example by low-dose cysteine, against acetaldehyde toxicity are insufficient to protect (or to bind acetaldehyde directly) upper gastrointestinal tract mucosa from the high acetaldehyde exposure during active smoking.

The present invention provides considerable advantages. The compositions comprising substances capable of binding aldehyde(s) can be used to decrease the risk of developing cancer of the mouth. In particular, the compositions according to the invention can be used for heavy smokers. The average amount of saliva excreted by a human is 1.5 litres a day. The areas of influence of the aldehyde(s) contained in the saliva include the mouth, the pharynx, the oesophagus, and the stomach. The compositions of the present invention are capable of decreasing the risk of developing cancer of all these areas.

An advantage of the aldehyde-binding substances, for example cysteine is, that the binding of harmful aldehydes is not limited only to aldehydes, but they are able to bind also other harmful and toxic compounds of tobacco smoke dissolved into saliva.

In the following, the present invention is examined more closely with the aid of a detailed description and examples.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows *in vivo* salivary acetaldehyde after ethanol ingestion in smokers (without concomitant smoking) and in non-smokers.

Figure 2 shows *in vivo* salivary acetaldehyde after ethanol ingestion in smokers (with concomitant smoking) and in non-smokers. Differences between acetaldehyde concentrations are significant at all time points from 40 to 160 min ($p \leq 0.05$).

Figure 3 shows salivary acetaldehyde in smokers after smoking one cigarette (without concomitant alcohol drinking).

Figure 4 shows the salivary acetaldehyde after 5 min smoking with placebo, and with 1.25 mg, 2,5 mg, 5 mg or 10 mg cysteine tablets.

Figure 5, 6 and 7 show various ways of attaching the preparation to a cigarette or cigar.

Figure 8 shows a holder which keeps the preparation in contact with saliva during smoking and through which tobacco smoke is inhaled.

Figure 9 and 10 show the impregnation of a holder or the surface of a holder with aldehyde binding substances.

Figure 11 shows the impregnation of a filter or the surface of a filter of a cigarette with aldehyde binding substances.

DETAILED DESCRIPTION OF THE INVENTION

"The aldehyde-binding substance" refers to a compound comprising one or more free sulphhydryl groups and/or one or more amino groups. According to the disclosure preferred compounds have one or more free sulphhydryl groups and one or more amino groups. By amino groups are meant $-NH_2$, -N, -NH- and NH_3^+ groups.

The "aldehydes" comprise C_1 - C_4 aldehydes potentially containing a double bond in the hydrocarbon chain. Examples of these aldehydes include formaldehyde, acetaldehyde, crotonaldehyde and acrolein, acetaldehyde being particularly important.

Although, we refer specifically to acetaldehyde in the following description, it should be understood that other C_1 - C_4 aldehydes are also, *mutatis mutantis*, considered.

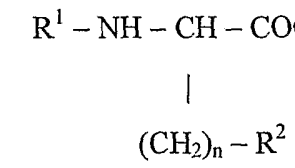
"The aldehyde-binding substance" refers also to compounds that are converted in mouth to an aldehyde binding substance. Such compounds are for example methionine and cystine.

"The binding of acetaldehyde" refers to a chemical reaction between the acetaldehyde and the compound that has a free sulphhydryl and amino group, wherein the acetaldehyde jointly with the "acetaldehyde-binding substance" forms a larger molecule, and water can be formed in the reaction. For example, when reacting with cysteine, the acetaldehyde binds itself both to the sulphhydryl and the amino group and forms 2-methyl-L-thiazolidine-4-carboxylic acid and water. The acetaldehyde can bind itself to the amino group of almost any protein, whereby Schiff's base or a 2-methyl-imidazole ring is formed.

Preferred compounds according to the disclosure are cysteine, its derivatives, compounds that are converted to cysteine and other compounds that function in a similar manner. Suitable substances for the use according to the disclosure are in particular cysteines and N-acetyl-cysteines, preferably L- and D-cysteines.

Preferred aldehyde-binding substances are naturally those that are not harmful for humans or which do not form harmful substances from aldehyde by chemical binding. It is also of advantage, if the compounds do not have unpleasant taste or smell.

Suitable compounds for binding aldehydes, in particular acetaldehyde in saliva also include the compounds according to the formula:



wherein

R^1 is hydrogen or an acyl group with 1-4 carbon atoms,

R^2 is a sulphhydryl or sulphonic group

n is an integer of 1 or 2.

Advantageously, in a reaction of the acetaldehyde binding compounds according to the disclosure with acetaldehyde, a Shiff's base is formed. The acetaldehyde binding molecule should contain one or more free amino groups and one or more free –SH groups. When the –SH group is at a suitable place of the molecule, it facilitates the forming of a Shiff's base and stabilizes the formed adduct.

Amino acids or other compounds that suitably bind aldehyde, in particular acetaldehyde comprise one or more free sulphhydryl (SH) group and amino ($-NH_2$, -N, -NH- or NH_3^+) group and comprise:

L-cysteine,

D-cysteine,

Cystine,

Cysteic acid,

Cysteine glycine,

Threo or erythro-β-phenyl-DL-cysteine,

β-tetramethylene-DL-cysteine,

Methionine,

D-penicillamine and its dipeptides with N-terminals,

Semicarbazide,

Reduced glutathione,

β-mercaptoethylamine,

D,L-homocysteine,

N-acetylcysteine,

L-cysteinyl-L-valine,
β,β-tetramethylene-DL-cysteine,
Cysteinyl-glycine,
Mercaptoethylglycine,
Tre-(5)- β-phenyl-DL-cysteine,
Erythro-β-phenyl-DL-cysteine,
Thiaminhydrochloride,
Mercaptanes.

The effect of some of the acetaldehyde-binding or other aldehyde-binding substances may be improved by vitamins, such as L-ascorbic acid.

The aldehyde-binding compounds according to the present invention should be non-toxic. Compounds suitable for the preparations according to the present invention should cause no health hazard in the amounts used in the invention.

It is also of advantage, if the compounds do not have unpleasant or very strong taste or smell. It is possible to mask the unpleasant taste of the effective compound by using suitable sweeteners and flavourings, but by using compounds having mild and/or pleasant taste it is possible to keep the composition simple, and its production is easier. Another way of decreasing the significance of the taste of the compounds is to use them in as small amounts as possible.

Tobacco can be used by smoking, chewing and dipping and snuffing. According to our studies, especially smoking seems to cause the formation of acetaldehyde in the mouth. Smoking in connection with the present invention means typically the use of cigarettes or cigars or alternatively pipe smoking.

"The short-term binding of acetaldehyde" (or other aldehydes) means that acetaldehyde formed during smoking is bound immediately and that the binding effect lasts as long as one cigar or cigarette is smoked or a few minutes longer. The binding effect lasts preferably at least 5 minutes, more preferably at least 10 minutes, most preferably at least 15 minutes.

Cigar smoking may last longer than cigarette smoking and therefore a preparation capable of binding acetaldehyde longer than 15 minutes is of advantage. However, the time is preferably shorter than 30 minutes. Alternatively, a person smoking a cigar may use more than one preparation during smoking of one cigar.

The preparation according to the present disclosure should be able for the release of the acetaldehyde (or other aldehydes) binding substance to saliva at the conditions prevailing in the mouth within less than 30 minutes and preferably within less than 15 minutes from the point of time when the preparation is contacted with the saliva. Acetaldehyde binding substances should thus be released within 0 – 5 minutes, more preferably within 0 – 10 minutes, most preferably within 0 – 15 minutes from the point of time when the preparation is contacted with the saliva. The release of acetaldehyde binding substances lasts preferably essentially the time of smoking of one cigar or cigarette i.e. the time of actual smoking and a couple of minutes longer.

"A harmful/carcinogenic content of acetaldehyde" in the human mouth, oesophagus, stomach, and large intestine is about 20-800 μmol/l of saliva, although it is difficult to define an amount of acetaldehyde, which would not be harmful. Such a harmful or carcinogenic content of acetaldehyde in the human mouth can be obtained in connection with for example smoking and/or alcohol drinking.

Keeping the acetaldehyde (or other aldehydes) content essentially lower than without the use of the preparation of the present invention means keeping the acetaldehyde content of saliva at a level that is at least 20%, preferably at least 40%, more preferably at least 60 %, and most preferably at least 80% lower than when not using the composition.

"In connection with smoking" herein refers to the period of time that begins from starting to smoke and ends, when smoking is stopped and 1 or 2 minutes before and after the actual smoking.

"A local preparation that is placed in the mouth" refers to all preparations that are sucked or chewed in the mouth or that may be placed between the cheek, the lip or the tongue and the gum (gingiva), and in which the release of the substance is intended to have a local

effect in the mouth. Preferably the preparation has effect also in the pharynx, the oesophagus or the stomach.

The term "composition" means here the composition comprising the effective substance(s) optionally admixed with a suitable carrier. The composition may be in the form of a local preparation suitable for use in mouth.

A local preparation according to the invention may be selected from the group of chewable or sucking tablets, buccal tablets, sublingual tablets, candies, pastilles, chewing gums, bubble gums, gels and lozenges.

The compounds that are used in the preparation that binds aldehydes, in particular acetaldehyde, can be compounds comprising one or more free sulphhydryl and amino groups.

In addition to the acetaldehyde-binding, so-called effective substance(s), the preparation comprises preferably at least one carrier substance that does not hinder or facilitates the release of the effective substance. It is preferred that the preparation has a form that facilitates keeping it in the mouth when smoking. The preparation may be circular or oval, convex, ring-formed and small enough and have a form that does not harm or change the smoking action.

The preparation may be put to the mouth during smoking or it may be attached by a suitable way to the tobacco product. The preparation may be kept attached to the tobacco product during smoking or it may be detached from the tobacco product and put to the mouth when starting to smoke.

It is of advantage, if the amount of the effective substance can be kept as low as possible, since there is then no or minor need to mask the taste of the compound, if the taste of the substance is unpleasant. The person using the composition need not consume too high concentrations of the compound. The preparation will also be less expensive.

The preparation of the present invention comprises preferably 1 to 300 mg aldehyde-binding, in particular acetaldehyde-binding substances, more preferably the amount is 1 to

250 mg, still more preferably 1 to 200 mg, even more preferably 1 to 150 mg, most preferably 1 to 100 mg. Higher amounts are specifically preferred when the aim is to bind various aldehydes in addition to acetaldehyde. The amount may be lower, if the aim is, in particular, to bind acetaldehyde.

According to a preferred embodiment of the invention the preparation of the present invention comprises 1 – 50 mg, more preferably 5 - 30 mg, more and more preferably 5 – 10 mg, or even 1 – 5 mg, typically 10 –20 mg, or 1 – 20 mg, in some embodiments 15 – 20 mg aldehyde-binding, in particular acetaldehyde-binding substance or substances.

The amount of the substances may preferably be higher, if the preparation is kept attached to the tobacco product during smoking as compared to, when the preparation is put to the mouth when starting to smoke.

Within the scope of the present invention are in addition to the above-disclosed preparations also other preparations and compositions used with tobacco products, which are able to release aldehyde-binding substances to saliva during smoking.

For example, a composition comprising the effective substance(s) may be concentrated and/or dried and/or impregnated to a tobacco product, to a filter or to a holder. The composition is preferably attached to that part of a tobacco product, filter or holder, which is put to the mouth when smoking. This may be about 1 to 10 mm from the tip of the tobacco product. Advantageously, the composition is attached to the surface of the tobacco product, filter or holder. This means that the concentration of the aldehyde-binding substance(s) is preferably higher on the surface of a tobacco product compared to the concentration inside of the tobacco product, filter or holder. The composition may, for example, be concentrated and/or dried and/or impregnated on the surface of the paper of a tobacco product, or filter or on the surface of a holder. The paper of a tobacco product may be protected by nonporous material not to let the aldehyde-binding substances to become absorbed into the paper and through the paper to the tobacco product or filter or holder. Alternatively the composition may be impregnated to the surface area of a tobacco product, to a filter or to a holder. The area may extend 1 or 2 mm from the surface towards the inside of the tobacco product, filter or holder.

The impregnated filter may also be separate from the tobacco product and may, for example, be attached to the tobacco product or located into a holder of a tobacco product.

The amount of aldehyde-binding substances may in these applications preferably be higher than in a preparation kept in the mouth. The amount of aldehyde-binding substances may be more than 5 mg, preferably more than 10 mg, more preferably more than 20 mg, most preferably more than 30 mg, even more preferably more than 50 mg per one tobacco product or filter or holder. Smaller amounts are preferred, if the composition is concentrated and/or dried and/or impregnated only to the surface of a filter, a tobacco product or a holder.

In addition to the effective substance(s), the composition may comprise:
1. pharmaceutically acceptable diluents (fillers, bulking agents), 2. sweetening agents such as sugars and sugar alcohols, 3. flavouring agents and 4. lubricants/glidants. Sugars may comprise for example sucrose, fructose or glucose or a combination of these. Sugar alcohols may comprise mannitol, sorbitol, maltitol, lactitol, isomalt or xylitol or a combination of these. Preferably, none of the additives reacts with other ingredients in the preparation. A preferable sweetening agent is mannitol, because it is not very sweet and its amount in the preparation can be quite high and thus its acts at the same time as a diluent.

Flavouring agents may comprise for example spearmint, peppermint, menthol, citrusfruit, eucalyptus or aniseed or a combination of these.

The preparation may comprise also other components, such as agents masking oral malodor, agents acting as breath freshener and/or agents preventing dental caries, or the preparation may comprise vitamins. The preparation may comprise also agents enhancing the excretion of saliva. However, these additional components should not prevent the quick release of the aldehyde binding substance to the saliva. As described here earlier, the preparation should release aldehyde binding substance so effectively that an essential amount of aldehyde is bound in saliva, before aldehyde affects the mucous membrane cells in mouth.

According to one preferred embodiment of the present invention the preparation (for example one tablet) may comprise or consist essentially of:

Aldehyde binding substance(s)	1 – 50 mg
Diluent(s)/Sweetening agent(s)	50 – 750 mg
Flavouring agent(s)	q.s.
Lubricant (s) (0.5 – 3 wt %)	5 – 25 mg

The preparation may be a sucking tablet comprising:

Acetaldehyde-binding substances	1 – 50 mg
sugar or sugar alcohol, such as mannitol	50 – 750 mg
Flavouring agent	q.s.
Magnesium stearate	5 – 25 mg

The composition is prepared by mixing the powder mass and compressing it into sucking tablets by well known methods.

If the amount of aldehyde-binding substances is increased, the amount of diluent(s)/sweetening agent(s) and flavouring agents may be increased also, since the taste of aldehyde-binding substances may be needed to be masked.

According to another preferred embodiment of the present invention the preparation may comprise or consist essentially of:

Aldehyde-binding substances	1 – 50 mg
Gum base comprising sweetening or other agents	500 – 1500 mg
Flavouring agent	q.s.
Lubricant (0.5 – 3 w- %)	5 – 30 mg

The gum base may comprise medical chewing gums (Morjaria, Y. et al., Drug Delivery Systems & Sciences, vol. 4, no 1, 2004.), which comprise natural or synthetic elastomers, plasticizers, waxes and lipids. Natural gum bases including chicle and smoked natural rubber are permitted by FDA. However, modern gum bases are mostly synthetic and include styrenebutadiene rubber, polyethylene and polyvinylacetate. The gum base makes up to 15 to 40 % of the chewing gum. The remainder consists of drug, sugar, sweeteners,

softeners, flavouring and colouring agents. The majority of chewing gum based drug delivery systems are manufactured using conventional processes. However, directly compressible powdered gums are modern alternatives for medical chewing gums. Pharmagum is a compactable new gum system. It is a mixture of polyol(s) and/or sugars with gum base. Formulation containing Pharmagums can be compacted into a gum tablet using conventional tablet presses. The manufacturing process is rapid and cheap. The amount of the gum base comprising sweetening agents may be in a preparation 50 – 500 mg, preferably 500 – 1500 mg.

Pharmagum S contains gum base and sorbitol, Pharmagum M contains gum base, mannitol and isomalt.

The preparation may be a chewing gum comprising:

Acetaldehyde-binding substances	1-50 mg
Pharmagum S	500 - 1500 mg
Flavouring agent	q.s.
Magnesium stearate (0.5 –3 w- %)	5 – 30 mg

The composition is prepared by mixing the powder mass and compressing it into chewing tablets.

The preparation may be a buccal tablet, which comprises:

Acetaldehyde-binding substances	1 -50 mg
Non-ionised macromolecules	5 – 25 mg
Ionising macromolecules	2 – 10 mg
Flavouring agent(s)	q.s.
Lubricants	0.5 -3w %

Non-ionised macromolecules include, for example, methylcellulose (MC), hydroxypropylcellulose (HPC), and hydroxypropyl-methylcellulose (HPMC), and polyethylene glycol (PEG). Ionising polymers include, for example, sodium carboxy-

methyl cellulose (NaCMC), alginic acid, sodium alginate, chitosan, polycarbophil (Noveon™), and carbomer (Carbopol™).

The preparation may also be a sublingual tablet, which comprises or consists essentially of:

Acetaldehyde-binding substances	1 -50 mg
Diluent(s)/Sweetening agent(s) q.s.	50 – 500 mg
Flavouring agent(s)	q.s.
Lubricants	0.5 – 3 w %

Diluents include, for example lactose, calcium phosphates, starch, carboxymethylcellulose, hydroxymethylcellulose. Sweetening agent can be for example mannitol or xylitol.

According to one preferred embodiment of the invention the preparations of the invention are provided in a kit comprising:

- *a plurality of cigars or cigarettes, and*
- a plularity of preparations comprising aldehyde binding substance or substances in an amount capable of binding aldehyde in saliva during smoking essentially to a level the aldehyde was before smoking.

Preferably, the preparation is capable of binding aldehyde in saliva during smoking of 1, 2 or 3 cigarettes or cigars.

The kit may comprise a tobacco pack or box for cigars or cigarettes connected with another box or pack for the preparations. The cigars or cigarettes and the preparations may be in the same or separate pack or box. The two packs or boxes may be separate or connected. Preferably, the kit comprises essentially the same or higher number of preparations as cigars or cigarettes.

According to another preferred embodiment of the invention the preparation may be attached to a tobacco product, such as a cigar, cigarette, holder or pipe. The preparation may be in any suitable form, such as chewing or sucking tablet, buccal tablet, sublingual tablet, candy, pastille, lozenge, chewing gum or gel. The preparation may

be of any suitable shape, such as circular, oval, convex, nail-like, cylinder-like, ring-like or rectangular.

According to one further preferred embodiment of the invention the preparation may be attached to a cigar, cigarette, holder or pipe in a detachable way. A person starting smoking may detach the preparation from the tobacco product by hands, by teeth or by some other way and chew, suck or keep the preparation in mouth, for example under the tongue or between the cheek and the gum thereby keeping the preparation in contact with saliva.

If the preparation is kept attached to the tobacco product during smoking, the preparation is preferably attached to that part of a cigar or cigarette (with or without a filter), holder or pipe, which is put to the mouth during smoking. This is because the preparation should come into contact with saliva during smoking. The preparation is preferably attached to the surface and near the tip or at the tip of a cigar, cigarette, pipe or holder. The preparation should also release the aldehyde-binding substances easily to saliva. The diameter of the preparation may be about the same as the diameter of a cigar or cigarette, about 3 to 10 mm, preferably about 3 to 8 mm. The preparation may be attached to the tip or near the tip of a cigar, cigarette, holder or pipe by a non-toxic adhesive-like material or by using a tape-like system. Adhesive-like materials suitable for foodstuff use are known to a person skilled in the art. Such materials are for example starch-based, sugar-based or protein-based adhesive-like materials.

According to one preferred embodiment of the invention the preparation may be attached to the tobacco product mechanically, for example by pressing it to the surface of the tobacco product. The preparation may comprise a projection with which the preparation is kept attached to the tobacco product, in particular to a cigar or cigarette. Alternatively the shape and size of the preparation may be suitable in order to keep it attached to the tobacco product, for example ring-formed or half-ring-formed.

According to another preferred embodiment of the invention the preparation may be kept attached to the cigar, cigarette, holder or pipe by using an arrangement for keeping the preparation in contact with the tobacco product, filter or holder. The arrangement may be a vehicle holding or carrying the preparation. The arrangement

may, for example, be a cylinder-formed part, which lengthens the tobacco product by about 1 to 5 mm. It may carry the preparation in such a way that the preparation becomes in contact with saliva when the tobacco product is put into mouth during smoking allowing at the same time the smoke go through the arrangement. The arrangement may be some inert material, such as plastic. The preparation and the arrangement may be attached to the tobacco products by the manufacturer of the tobacco products or by the smoker.

According to one further preferred embodiment of the invention a composition comprising aldehyde binding subtance(s) may be impregnated to that part of a cigar or cigarette (with or without filter), which is put to mouth when smoking. The composition may be impregnated also to a holder for cigarette or cigar. The composition may be impregnated also to a separate filter, which may be put in front of the tobacco product optionally with a holder. According to preferred embodiments of the invention the composition is impregnated and/or concentrated and/or dried to the surface of a cigar, cigarette, filter or to the surface of a holder, which is used when smoking. The composition may, for example, be impregnated directly to the surface of a cigar, cigarette or holder or into a suitable material, such as cellulose, which is attached to the surface.

A composition comprising aldehyde-binding subtance(s) and concentrated and/or dried and/or impregnated to a tobacco product, to a filter or to a holder, in particular to the surface of a cigar, cigarette, filter or to the surface of a holder, may be used as a solution or in solid form, for example as a powder optionally with or without a carrier. The composition may comprise the same components as the local preparation. It may comprise also a diluent, which may be any suitable, volatile diluent, preferably water, which is evaporated during the preparation procedure.

Administration of aldehyde-binding compositions

The content of aldehyde formed in saliva as a consequence of smoking can be decreased so that in connection with smoking, a preparation, preferably one or two

preparations at a time, is/are placed in the mouth, under the tongue or in the cheek, or between the cheek and gum for example, which at a suitable and preferably at a constant rate release(s) cysteine (or an aldehyde-binding agent having essentially the same effect as cysteine) continuously and preferably until one tobacco product is used. When starting the next tobacco product, a new aldehyde-binding preparation is placed in the mouth. The aldehyde content of saliva decreases by over 20%, preferably by over 40%, more preferably over 60%, typically by 60-80% compared to placebo. According to a preferred embodiment of the invention the preparation is able to decrease aldehyde content of saliva during the smoking of one cigar, cigarette or pipe to a level aldehyde was before smoking.

The use of aldehyde- binding preparation is repeated as many times as a new tobacco product is started. It is of advantage, if the preparation is placed in the mouth already before starting a new cigar, cigarette or pipe.

Preferably the amount of aldehyde-binding substance(s) in one preparation should be essentially sufficient to bind aldehyde in saliva to a level aldehyde was before smoking. If the aldehyde-binding composition is attached to a tobacco product, filter or holder, by an adhesive-type material, by an arrangement or by any other way or by concentrating, drying or impregnating the composition to the tobacco product, filter or holder, the amount of the effective substance should essentially be sufficient to bind aldehyde in saliva during the smoking of one tobacco product, preferably the amount should be at least 2, preferably at least 5, more preferably at least 10 times higher.

Examples

Example 1

A sucking tablet was prepared comprising:

Cysteine	20 mg
Mannitol (or equivalent sugar or sugar alcohol)	750 mg
Flavouring agent	q.s.

Magnesium stearate	10 mg

The composition was prepared by mixing the powder mass and compressing it into sucking tablets.

Example 2

Sucking tablets were prepared as in Example 1, but comprising 1.25 mg, 2.5 mg, 5mg and 10 mg cysteine.

Example 3

A chewing gum was prepared comprising:

Cysteine	20 mg
Pharmagum S, M or C	1000 mg
Flavouring agent	q.s.
Magnesium stearate	20 mg

The composition was prepared by mixing the powder mass and compressing it into chewing gums. Another composition was prepared comprising 500 mg Pharmagum S or M and 20 mg magnesium stearate.

Example 4

A buccal tablet was prepared comprising:

Cysteine	20 mg
Methocel	25 mg
Carbopol	7 mg
Flavouring agent	q.s.
Magnesium stearate	2 mg

The composition was prepared by mixing the powder mass and compressing it into buccal tablets.

Example 5

A sublingual tablet was prepared comprising:

Cysteine	10 mg
Mannitol	250 mg
Flavouring agent	q.s.
Magnesium stearate	5 mg

The composition was prepared by mixing the powder mass and compressing it into sublingual tablets.

Example 6

The preparation prepared in Example 1 was tested by two test persons. The acetaldehyde content of saliva of the test persons was measured before smoking and then after each 5 min during smoking, i.e. 0 min, 5 min, 10 min and 15 min after the test persons had started smoking. Both of the test persons smoked one cigarette at the same time collecting saliva to their mouth and sucking a placebo tablet. The smoking lasted 5 min. In the second test the test persons repeated the study by sucking a tablet comprising 20 mg cysteine.

Before smoking the acetaldehyde content of saliva was very low by both of the test persons. In the second test the acetaldehyde content had decreased to a non-measurable level already after first 5 minutes.

Example 7

Five smokers (age 29 ± 2.8) participated in the study, in which three cigarettes were smoked (wash-out periods between). During every cigarette smoking (in 5 min time) volunteers sucked blinded tablets containing placebo, 1.25 mg, 2.5 mg, 5 mg, 10 mg or 20 mg L-cysteine. Acetaldehyde was analysed from salivary samples gas chromatographically at 0, 5, 10, 20 min from the beginning of smoking.

L-cysteine tablets (5 mg, 10 and 20 mg) totally eradicated the tobacco-originated acetaldehyde from the saliva (see Figure 4). The mean salivary acetaldehyde concentrations immediately after smoking were 191.2±48.5 μM, 0μM, 0 μM, 0 μM with placebo, 5 mg, 10 mg and 20 mg L-cysteine tablets, respectively.

The study shows that already 5 mg of L-cysteine administered by melting–tablet totally inactivates carcinogenic acetaldehyde in the saliva during smoking. 1.25 mg L-cysteine tablet lowers the amount of acetaldehyde about to third compared to placebo.

Example 8

Sucking tablets, chewing gum, buccal tablet and sublingual tablets are prepared comprising 5 mg L-cysteine.

Example 9

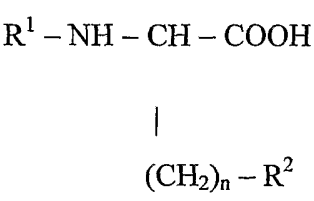
A cigarette (1) is prepared according to conventional methods. The cigarette may comprise a filter (2) or it may be without a filter. A cysteine comprising preparation (3) is prepared as disclosed here earlier. The shape of the preparation may be any suitable shape, such as circular, oval, convex, nail-formed, ring-formed, cylinder or rectangular. The preparation (3) is attached to the cigarette (1) by an adhesive-like material suitable for human use. As shown in Figure 5A the cysteine composition is in the shape of a ball attached to that part of the cigarette, which is put to the mouth when smoking, in Figure 5 B is shown the cigarette with the preparation as a cross-section. In Figure 6A the preparation (3) is at the tip of the cigarette (1) at that part of the cigarette, which is put into mouth when smoking. Figure 6B is a cross-section of the same. In Figure 7A the preparation (3) is rectangular and it is bent around the tip of the cigarette at that part of the cigarette (1), which is put to the mouth when smoking, Figure 7B is cross-section of the same. In Figure 8 a cylinder (5) is attached to the tip of the filter (2) of a cigarette (1). A preparation (3) comprising cysteine is located inside the cylinder. In Figure 9 a holder (4) or the surface of a holder is impregnated by cysteine (3). In Figure 10 a holder (4) or the surface of a holder is impregnated by cysteine comprising composition (3) and the shape of the holder is suitable for holding in particular a cigar. In Figure 11 the filter (2) or the surface of a filter of the cigarette (1) is impregnated by cysteine (3).

CLAIMS

1. Use of compounds, which are capable of binding aldehydes and comprise one or more free sulphhydryl and amino groups, for producing a preparation for locally binding aldehydes in saliva during smoking, said preparation comprising an effective amount of the aldehyde binding substance(s) and a non-toxic carrier, said carrier allowing for the release of the aldehyde binding substance(s) during the smoking of one tobacco product.

2. The use according to claim 1, **characterized** in that the carrier allows for the release of the aldehyde-binding substance to saliva at the conditions prevailing in the mouth within less than 30 minutes.

3. The use according to claim 1 or 2, **characterized** in that the preparation comprises one or more compounds according to the formula:



wherein
R^1 is hydrogen or an acyl group containing 1 - 4 carbon atoms,
R^2 is a sulphhydryl group or sulphonic acid, and
n is 1 or 2.

4. The use according to any one of claims 1 to 3, **characterized** in that the preparation comprises one or more substances selected from the group comprising: L-cysteine, D-cysteine, cystine, cysteic acid, cysteine glycine, threo- or erythro-β-phenyl-DL-cysteine, β-tetramethylene-DL-cysteine, methionine, D-penicillamine and its N-terminal dipeptides, semicarbazide, reduced glutathione, β–mercaptoethylamine, D,L-homocysteine, N-acetylcysteine, L-cysteinyl-L-valine, β,β-tetramethylene-DL-cysteine, cysteinyl glycine, mercaptoethyl glycine, tre-(5)- β-phenyl-DL-cysteine, erythro-β-phenyl-DL-cysteine, thiamine hydrochloride and mercaptane.

5. The use according to any one of the preceding claims, **characterized** in that the preparation comprises an aldehyde-binding substance, to which the aldehyde binds itself both through a sulphhydryl and an amino group.

6. The use according to any one of the preceding claims, **characterized** in that the aldehyde-binding substance is selected from the group comprising L-cysteine, D-cysteine, a derivative of cysteine and a substance that is capable of converting to cysteine.

7. The use according to any one of the preceding claims, **characterized** in that the aldehyde is acetaldehyde.

8. The use according to any one of the preceding claims, **characterized** in that the carrier comprises substances selected from the group comprising pharmaceutically acceptable diluents, sweetening agents, flavouring agents and lubricants/ glidents.

9. The use according to any one of the preceding claims, **characterized** in that the composition is in the form of a preparation selected from the group comprising chewable tablets, buccal tablets, sublingual tablets, candies, pastilles, lozenges, chewing or bubble gums and gels.

10. A method for decreasing the risk of cancer of the mouth and pharynx, larynx, oesophagus and stomach, **characterized** in that the aldehyde in saliva is locally bound during smoking by using a composition comprising an effective amount of aldehyde binding substance(s) and a carrier allowing for the release of the aldehyde binding substance(s) to saliva at the conditions prevailing in the mouth.

11. The method according to claim 10, **characterized** in that the composition lowers the amount of aldehydes during smoking of one cigar, cigarette or pipe essentially to the level of aldehydes in saliva before smoking.

12. The method according to claim 10 or 11, **characterized** in that the carrier comprises substances selected from the group comprising pharmaceutically acceptable diluents, sweetening agents, flavouring agents and lubricants/ glidents.

13. The method according to any one of claims 10 to 12, **characterized** in that the composition is in the form of a preparation selected from the group comprising chewable tablets, buccal tablets, sublingual tablets, candies, pastilles, lozenges, chewing or bubble gums and gels.

14. The method according to any one of claims 10 to 13, **characterized** in that in connection of smoking at least one preparation is placed in the mouth, said preparation releasing aldehyde-binding substance(s) to saliva essentially the time one tobacco product is used.

15. The method according to any one of claims 10 to 14, **characterized** in that the composition is attached to a tobacco product, filter or to a holder.

16. The method according to claim 15, **characterized** in that the composition is attached to that part of a tobacco product, filter or holder, which is put to the mouth when smoking.

17. The method according to claim 15 or 16, **characterized** in that the composition becomes in contact with saliva during smoking, said composition releasing aldehyde-binding substance(s) to saliva essentially the time one tobacco product is used.

18. The method according to any one of claims 15 to 17, **characterized** in that the composition is detachable from the tobacco product, filter or holder.

19. A composition comprising aldehyde-binding substance(s), **characterized** in that the composition is attached to a tobacco product, filter or holder for binding aldehyde during smoking in saliva.

20. The composition according to claim 19, **characterized** in that the composition is attached to that part of a tobacco product, filter or holder, which is put to the mouth when smoking.

21. The composition according to claim 19 or 20, **characterized** in that the composition comprises substances selected from the group comprising pharmaceutically acceptable diluents, sweetening agents, flavouring agents and lubricants/ glidents.

22. The composition according to any one of claims 19 to 21, wherein the composition is in the form of a preparation selected from the group comprising chewable tablets, buccal tablets, sublingual tablets, candies, pastilles, lozenges, chewing gums and gels.

23. The composition according to any one of claims 19 to 22, **characterized** in that the composition is attached to a tobacco product, filter or to a holder with or without an adhesive like-material.

24. The composition according to any one of claims 19 to 23, wherein the composition is attached by using an arrangement for keeping the composition in contact with a tobacco product, filter or holder.

25. The composition according to any one of claims 19 to 24, wherein the composition is attached by impregnating and/or concentrating and/or drying the composition to a tobacco product, filter or holder

26. The composition according to any one of claims 19 to 25, wherein the concentration of the aldehyde-binding substance(s) is higher on the surface of a tobacco product, filter or holder than in the inside of the tobacco product, filter or holder.

27. The composition according to any one of claims 19 to 26, wherein the composition is attached to the surface of a tobacco product, filter or holder.

28. A kit comprising:

- a plurality of cigars or cigarettes, and

- a plularity of preparations comprising aldehyde binding substance(s) in an amount capable of binding aldehyde in saliva during smoking essentially to a level the aldehyde was before smoking.

29. The kit according to claim 28, wherein the preparation is capable of binding aldehyde in saliva during smoking of 1, 2 or 3 cigars or cigarettes.

30. A tobacco product, filter or holder, which comprises
- a tobacco product, filter or holder; and
- a composition attached to a tobacco product, filter or holder, said composition comprising aldehyde binding substance(s) in an amount capable of binding aldehyde in saliva during smoking essentially to a level the aldehyde was before smoking.

31. The tobacco product according to claim 30, **characterized** in that the composition is attached to that part of a tobacco product, filter or holder, which is put to the mouth when smoking.

32. The tobacco product according to claim 30 or 31, wherein the composition comprises substances selected from the group comprising pharmaceutically acceptable diluents, sweetening agents, flavouring agents and lubricants/ glidents.

33. The tobacco product according to any one of claims 30 to 32, wherein the composition is in the form of a preparation selected from the group comprising chewable tablets, buccal tablets, sublingual tablets, candies, pastilles, lozenges, chewing gums and gels.

34. The tobacco product according to any one of claims 30 to 33, wherein the composition is detachable from the tobacco product, filter or holder.

35. The tobacco product according to any one of claims 30 to 34, wherein the composition is attached with or without an adhesive- like material.

36. The tobacco product according to any one of claims 30 to 35, wherein the composition is attached by using an arrangement for keeping the composition in contact with a tobacco product, filter or holder.

37. The tobacco product according to any one of claims 30 or 36, wherein the composition is attached by impregnating and/or concentrating and/or drying the composition to a tobacco product, filter or holder.

38. The tobacco product according to any one of claims 30 to 37, wherein the concentration of the aldehyde-binding substance(s) is higher on the surface of a tobacco product, filter or holder than in the inside of the tobacco product, filter or holder.

39. The tobacco product according to any one of claims 30 to 38, wherein the composition is attached to the surface of a tobacco product, filter or holder.

40. The tobacco product according to any one of claims 30 to 39, wherein the tobacco product is a cigar, a cigarette or a pipe.

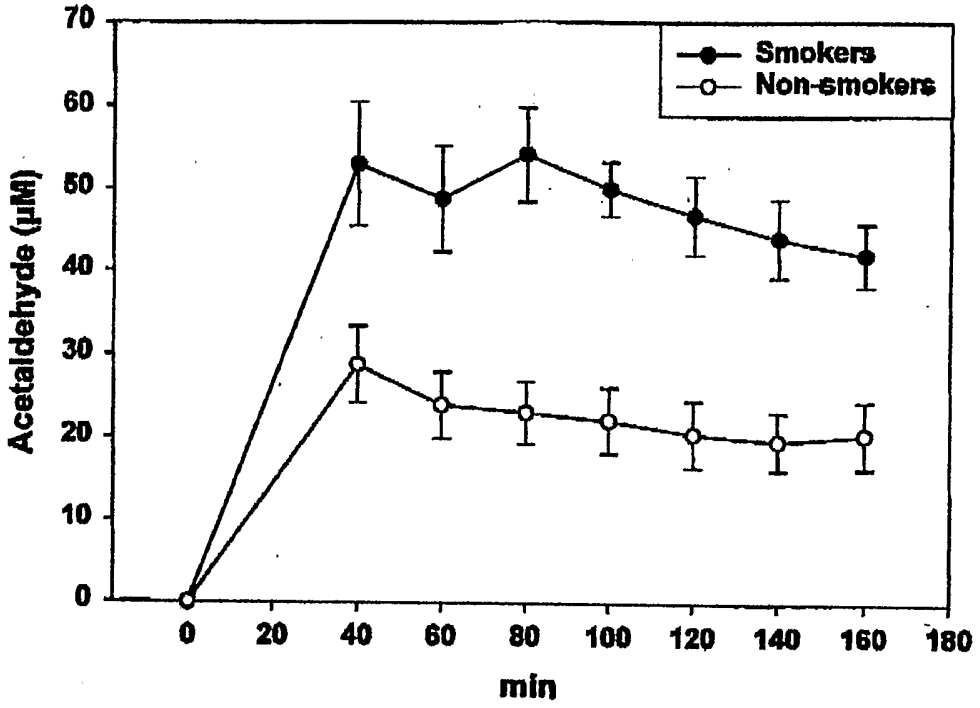

Smokers
Non-smokers
Acetaldehyde (µM)
70
60
50
40
30
20
10
0
0
20
40
60
80
100
120
140
160
180
min

Fig. 1

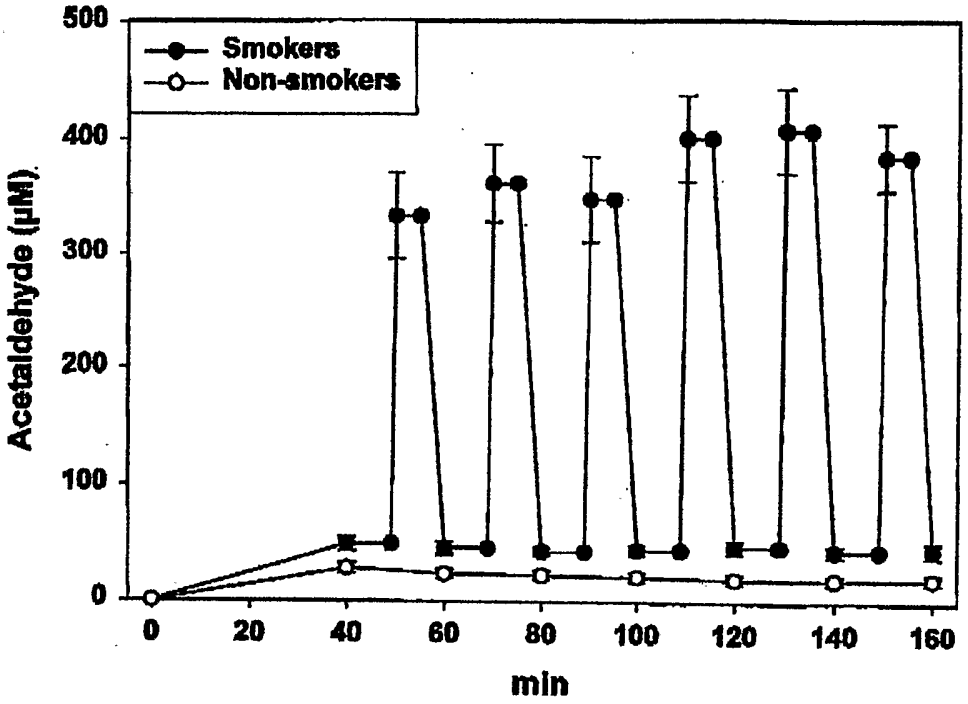

Smokers
Non-smokers
Acetaldehyde (µM)
500
400
300
200
100
0
0
20
40
60
80
100
120
140
160
min

Fig. 2

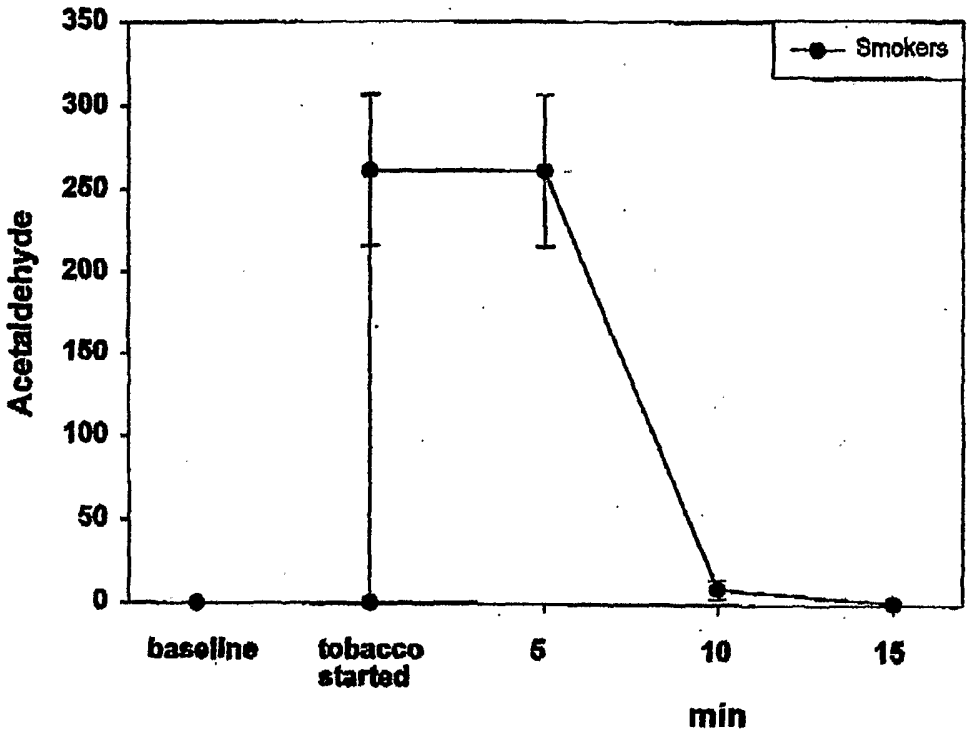

Smokers
Acetaldehyde
350
300
250
200
150
100
50
0
baseline
tobacco started
5
10
15
min

Fig. 3

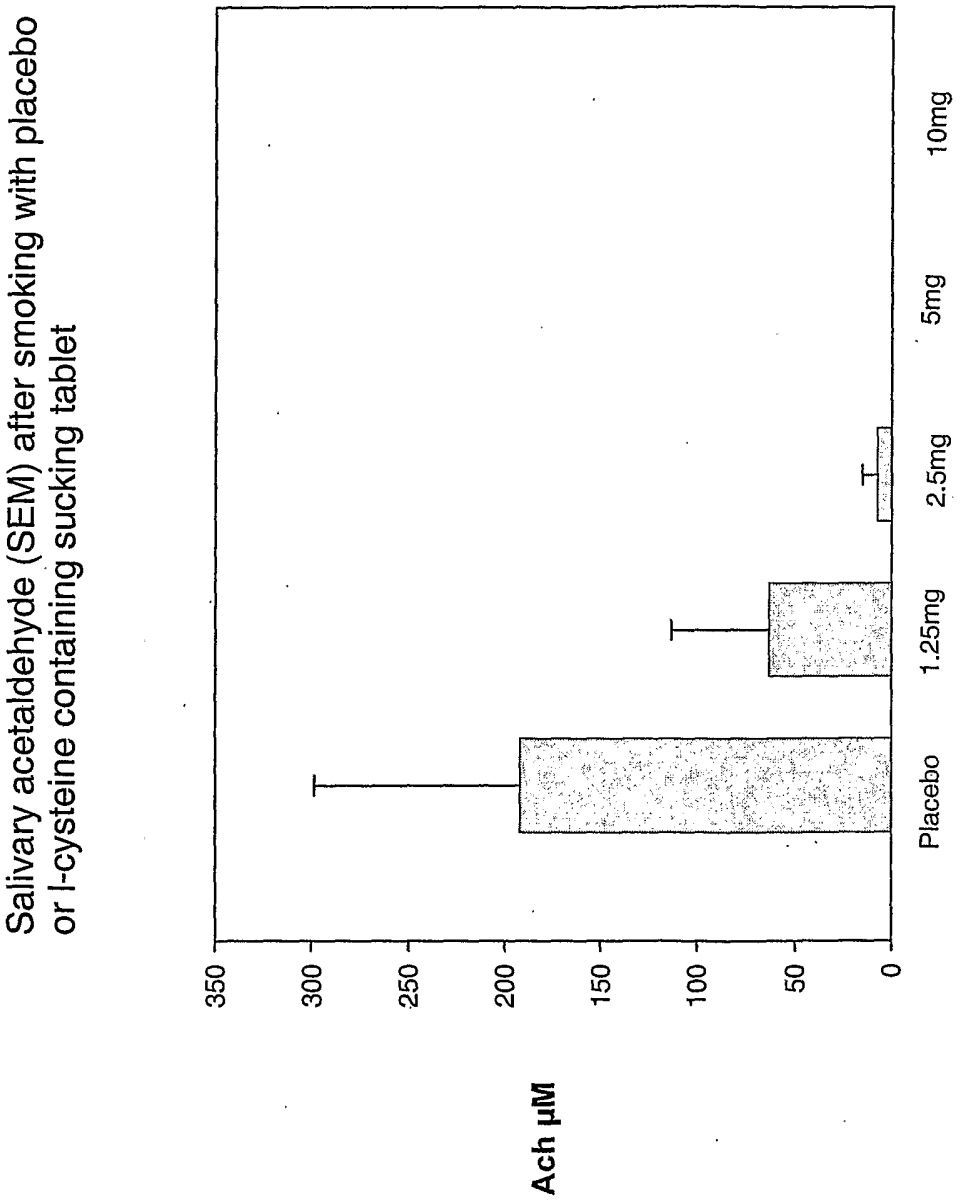

Salivary acetaldehyde (SEM) after smoking with placebo or l-cysteine containing sucking tablet
Ach µM
350
300
250
200
150
100
50
0
Placebo
1.25mg
2.5mg
5mg
10mg
l-Cysteine concentration

Fig. 4

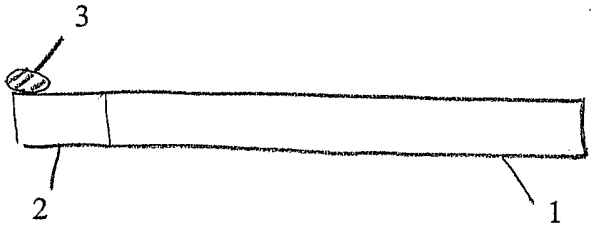


Fig. 5A

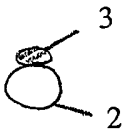


Fig. 5B

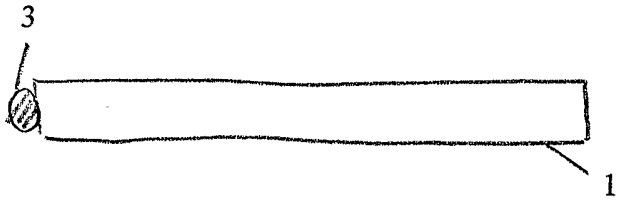


Fig. 6A

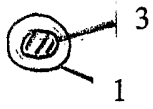


Fig. 6B

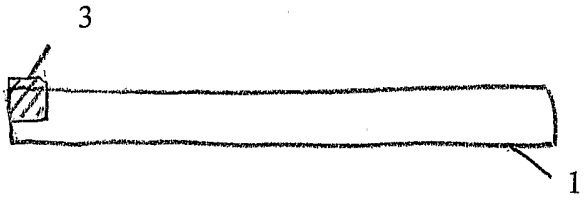


Fig. 7A

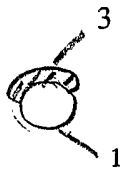


Fig. 7B

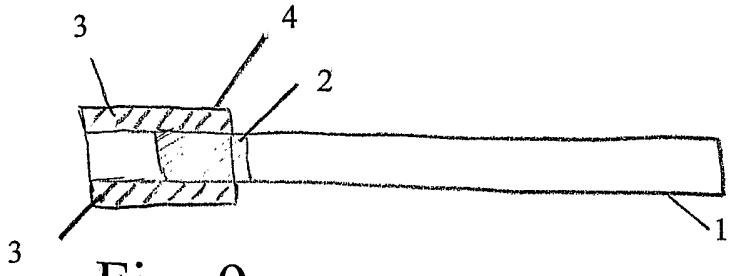


Fig. 9

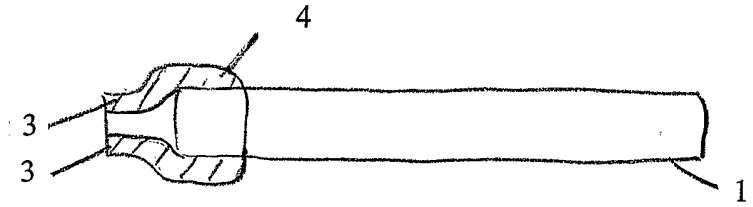


Fig. 10

Fig. 11

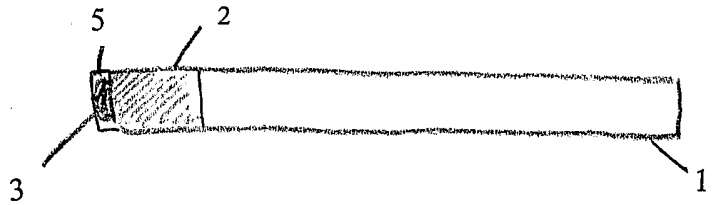


Fig. 8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 2005/000429

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: A61K, A24D, A24B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CHEM ABS DATA, BIOSIS, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 0236098 A1 (LICENTIA LTD), 10 May 2002 (10.05.2002), See especially page 3, lines 23-34; page 5, lines 10-11; page 9, lines 9-20; page 16, lines 7-11; page 17, lines 3-33; the claims --	1-24,26-36, 38-40
X	WO 9915035 A1 (THIONE INTERNATIONAL, INC.), 1 April 1999 (01.04.1999), See the examples and claims --	19-21,23, 25-32,35, 37-40
X	EP 1238594 A2 (PERA, IVO), 11 Sept 2002 (11.09.2002), See the claims --	19-21,23, 25-32,35, 37-40

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 February 2006	22-02-2006
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Per Renström/Els Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 2005/000429

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4532947 A (JANE R. CASELEY), 6 August 1985 (06.08.1985), See especially column 2, lines 53-57; column 4, lines 6-61 ---	19-21,23, 25-32,35, 37-40
X	US 5060672 A (SáNDOR IRIMI ET AL), 29 October 1991 (29.10.1991), See especially Example 1 and the claims --- --------	19-21,23, 25-32,35, 37-40

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI2005/000429

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 10-18
because they relate to subject matter not required to be searched by this Authority, namely:

See next sheet.

2. ☒ Claims Nos.: 1-2, 5-40
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

See next sheet.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Continuation of Box No. II.1:

Claims 10-18 relate to a (prophylactic) method of treatment of the human or animal body by therapy (see Rule 39.1(iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds.

Continuation of Box No. II.2:

Claims 1-2 and 5-40 relate to an extremely large and undefined number of possible compounds. A meaningful search over the whole of the claimed scope is therefore impossible. Consequently, the search has been carried out only for those parts of the claims related to the compounds defined in claims 3 and 4, in combination with the claimed use and alleged effects.

Specifically, claims 1-2 and 5-40 relate to products defined by reference to several desirable properties, namely the following:
(1) the various expressions relating to "aldehyde binding substance(s)", the ability of the compounds to bind aldehydes, and the ability of the carrier or preparation to release the aldehyde binding substance(s);
(2) that the carrier should be non-toxic.

Chemical compounds are not clearly defined merely by reference to a result to be achieved, e.g. the binding of aldehydes. The further specification that the compounds comprise on or more free suphhydryl and amino groups is not sufficient for the compounds to be clearly and concisely defined, since there is an extremely large number of such compounds. The expression "derivative of cysteine" (claim 6) is also unclear in its scope. Claims 1-2 and 5-40 therefore lack clarity and conciseness within the meaning of Article 6 PCT.

Moreover, the application provides support within the meaning of Article 6 PCT and / or disclosure within the meaning of Article 5 PCT for only a very small proportion of the claimed scope, namely the parts of the claims related to the compounds defined in claim 3.

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